REMARKS

Claims 1 to 4 and 14 are pending. Claims 5 through 13 are canceled. Claim 1 is amended. Applicant reserves the right to pursue the canceled claims in a divisional application. In the November 20, 2007 Examiner Interview, Examiner Saunders stated that claim 14 would be subject to restriction.

Support for the amendment to claim 1 may be found, for example, (1) in Example 5 of the application, which cites Bogoch *et al.*, Protides of Biological Fluids, 30, 337-352 (1983) as showing that antimalignin antibody introduced intravenously in Wistar rats bound preferentially *in vivo* to malignant glioma cells, (2) in Example 1 of the application, which shows that 50 µl of 10 µg/ml antimalignin antibody is cytotoxic to glioblastoma brain cancer cells growing on the wall of tissue culture flasks (*see* Figure 1j-l, Appln. at 8), and (2) in Example 6 and Figure 2 of the application, which illustrate inhibition of growth of small cell lung carcinoma cells *in vitro* inhibited by anti-malignin antibodies in the range of picograms per cell thereby demonstrating cell killing activity at surprisingly low concentrations. Additionally, for example, Example 8 provides a detailed description of how one of skill in the art may practice claim 1 as amended by administering doses of malignin subcutaneously to stimulate the immune system of a subject to produce antimalignin antibodies that inhibit glioma cancer cells. Appln. at 17-18.

Enablement Rejection of Claims 1-4

*1. **Malignin is an about 10 KDa peptide in the Recognin family of oncopeptides***

In the final Office Action mailed September 24, 2007, the Office maintains an enablement rejection of claims 1-4 because Example 8 in the specification allegedly "teaches one how to stimulate production of anti-recognin antibody, not of anti-malignin antibody." Office Action at 2. The Office bases its reasoning on the allegation that "Recognin is a 250,000 Dalton glycoprotein that is a precursor of malignin" and that "malignin is inherently a 16-mer peptide of much lower molecular weight."

In the response of October 31, 2007 and the interview of November 20, 2007, Applicant demonstrated that the specification of the above-captioned application is clear that malignin is not a 16-mer peptide but is instead a peptide of about 89 amino acids with a mass of about 10 KDa that falls within the 10 KDa immunological family of recognin oncopeptides. *See* Appln. at 17 and U.S. Pat. No. 4,976,957 cols. 1-3, which is incorporated by reference in Appln. at 17.

Members of the family of recognin oncopeptides are each derived from an aglycoprotein precursor of about 250 KDa. *Id.* Additionally, the "anti-recognin" antibody of Example 8 is an antimalignin antibody that also binds to peptides identified in the recognin family of oncopeptides, for example, astrocytin, malignin, recognin M and recognin L. Appln. at 17.

Examiner Saunders requested in the November 20, 2007 interview that Applicant again provide citations from the specification establishing that (1) the malignin peptide is an about 89 amino acid peptide of about 10 KDa identifiable with the recognin family of oncopeptides, and (2) the anti-recognin antibody of Example 8 is an anti-malignin antibody that binds epitopes on the malignin and identically binds other recognin oncopeptides like recognin L and recognin M.

As discussed, Recognins are a family of peptides having molecular weights of about 8 to about 10 kDa. *See* Appln. at 5-6 ("When malignin was produced as the immunogenic fragment of the precursor it was thought to be a cell-type-specific cancer marker. It was only when similar 10K peptides with identical immunoreactivity were produced from MCF7 breast cancer cells (Recognin M) and from P3J lymphoma (Recognin L) that malignin appeared to be a more general cancer antigen.") Recognins are not the 250 kDa precursor of Malignin. Rather Recognin defines a family of peptides of about 10 KDa that includes malignin. The specification teaches that Recognins are all about 10 kDa, all share immunoreactivity, and all generate anti-Recognin antibodies that are similarly immunoreactive with the family of Recognin peptides. *See* Spec. at 17 and U.S. Pat. No. 4,976,957 cols. 1-3.

The specification specifically teaches that malignin, Recognin M and Recognin L share immunological specificity. Spec. at 17. The specification further incorporates U.S. Patent No. 4,976,957 by reference when describing malignin, Recognin L and Recognin M. Spec. at 17. U.S. Patent No. 4,976,957 expressly teaches that "malignin, astrocytin, Recognin M and Recognin L are [all] Recognins." Col. 7, ll. 2-3. The patent further teaches Astrocytin is an about 8 KDa Recognin (col. 1, ll 37-38, 65), Recognin M is an about 8 KDa Recognin (col. 3, ll. 8-16), Recognin L is an about 8 KDa Recognin (col. 3, ll. 25-33) and malignin is an about 10 KDa Recognin (col. 2, ll. 32-39). For example, U.S. Patent No. 4,976,957 states concerning the isolation of malignin: "In a manner similar to that described above, another Recognin, called Malignin, is produced from artificial cancer cells, i.e., cancer cells grown in *in vitro*

fermentation. Malignin has a molecular weight of about 10,000 and similar but distinct amino acid residue composition to Astrocytin . . . ." *Id.*, col. 2, ll. 32-39.

Example 8 teaches the production of anti-malignin antibodies by subcutaneous administration of malignin, a 10 KDa peptide, not by administration of the 250 KDa precursor of malignin. Example 8 expressly teaches administration of any product that contains the immunological specificity of malignin to produce an immune response to malignin or other Recognin peptide (such as astrocytin). *See* Spec. at 17. The specification then incorporates U.S. Patent No. 4,976,957 by reference. Example 7 of U.S. Patent No. 4,976,957 expressly teaches administration of "1 mg. of Astrocytin or Malignin" injected into the toe pads of white male rabbits to produce antisera to astrocytin or malignin. Col. 24, ll. 16-19.

In view of the specification's clear teaching that malignin is an about 10 KDa peptide of about 89 amino acid residues and that anti-malignin antibodies that have both inhibitory and cytotoxic properties are produced when malignin is injected into a subject, the Applicant respectfully requests the Office withdraw its rejection of claims 1-4 based on the incorrect assumption that malignin is a 16 amino acid residue peptide (malignin is a much larger 10 KDa peptide) and the antibody of Example 8 is not antimalignin (the anti-recognin antibody of Example 8 is produced by injection of malignin in a subject).

2. Spitler and Ezell Demonstrate the Practicability of the Claims

The Office further proposes that despite the step-wise presentation in Example 8 of a method of administering malignin to a subject to inhibit glioma cells and other cancers, the specification does not enable one of skill in the art to practice the claims because "cancer vaccines don't work." Office Action at 5-6. The Office cites Ezell (Jour. of NIH Res. vol. 7, pp. 46-49, January 1995) and Spitler (Cancer Biotherapy, vol. 10, no. 1, pp. 1-3, 1995) for this proposition. Office Action at 5-6. As discussed in the Response of October 31, 2007 and the Examiner Interview of November 20, 2007, Spitler and Ezell do not teach that the method of inhibiting glioma cells presented by the Applicant will not work. In fact, Spitler and Ezell provide the skilled artisan with an expectation of success of the present claims because the Applicant has provided the very information that Spitler and Ezell teach as necessary to identify a cancer vaccine.

For example, the Office asserts Spitler concludes that cancer vaccines as of 1995 did not work because "tumor antigens have not been well characterized and because conventional adjuvants have been used[, rather than better-designed adjuvants]." Office Action at 5. The Office finds "Spitler further teaches that cancer vaccines may be made to work when the tumor antigens have been chemically characterized and/or when improved adjuvants have been developed." *Id.*

As raised by the Applicant in the November 20, 2007 interview, Spitler expects cancer vaccines to work when they have been developed to the very point that the Applicant has provided in the present application. *See, e.gi,* Spitler at 46, right column ("The identification of tumor-specific antigens has transformed the field of tumor immunology, which was once viewed with skepticism by other immunologists."). Spitler notes that past cancer vaccines have been based on cell extracts or whole proteins but that as specific antigens have been characterized, the characterized antigens have provided the specificity necessary to elicit an immune response sufficient to inhibit cell growth. *Id.* ("[W]e now know quite well how some antigens are presented and how they are recognized by antibodies and T cells.")

Applicants have provided the very teaching noted by Spitler to have resulted in cell inhibitory vaccines. *See, e.g.*, Spitler at 47 (LAKs shrink tumors in about 20 percent and TLSs shrink tumors in about one-third of melanoma patients) and 48 (MAGE-1 and MART-1 vaccines ready for initial testing in humans). Applicants have characterized with specificity an 89 amino acid peptide (malignin) that is immunoreactive with antibodies naturally produced in cancer patients and correlated with patient survival. Applicants have demonstrated a strong immune response to the peptide upon subcutaneous injection. Applicants have demonstrated binding of the characterized antibody in rat brains *in vivo* and inhibition of cancer cells and complement-dependent killing of glioma cancer cells in human serum. Applicants have, therefore, provided extensively more data than Spitler requests for producing a cancer vaccine. *See, e.g.*, Spitler at 49 ("We are convinced that essentially all tumors have between five and 10 different antigens that can be recognized by cytotoxic T cells . . . .").

Likewise, the Office notes Ezell's suggestion that cancer antigens be more specifically characterized using heat shock proteins because uncharacterized cancer extracts don't work. Office Action at 8. As discussed above, the Applicant has characterized the malignin peptide

with specificity and as such do not need further characterization using heat shock proteins. As such, no additional experimentation is necessary. The specific malignin peptide is described. A method of subcutaneous injection of the malignin peptide is described. A strong immune response to the subcutaneous injection of malignin is established. Binding *in vivo* is established. And clear data for inhibition and cytotoxicity of cancer cells is provided. Ezell's requirements are satisfied for sufficient characterization of the malignin peptide as a cancer antigen.

For example, Ezell states: "Cancer vaccines have finally reached the stage in technological development where commercial development can be envisioned. Due to the development of monoclonal antibody technology, scientists have now identified and characterized tumor associated antigens and determined their tissue distribution." Ezell at 2. "Almost everyone in this field has had the experience of seeing a dramatic regression of metastatic disease following vaccine therapy." *Id.*

Both Spitler and Ezell provide data on properly characterized cancer antigens that have successfully induced inhibitory responses. *See* Spitler at 47-49, Ezell at 2 ("Investigators who have reported clinical successes with vaccine therapy in large series of patients include Berd, D. *et al.*, Bystryn, J.C., Hersey, P. *et al.*, Mitchell, M.S. *et al.*, Morton, D.L. *et al.*, Seigler, H.F. *et al.*, and Wallack, M.K., *et al.*"). While the discussed vaccines are not presented as perfect vaccines, they each are shown to provide inhibition in certain circumstances or patients. Enablement does not require inhibition in all patients. *See, e.g.,* MPEP § 2107.03(V) ("[I]t is improper for Office personnel to request evidence . . . regarding the degree of effectiveness.") Instead, the full scope of the claims must be enabled.

Claims 1-4, therefore, require inhibition of glioma cells. Complete remission is not required. Further, inhibition in all circumstances need not be demonstrated. *See, e.g.*, MPEP § 2164.02("A rigorous or invariable exact correlation is not required . . . ."). Instead, enablement requires inhibition to be shown in glioma cells wherein said inhibition can be practiced by one of skill in the art without undue experimentation. Both Spitler and Ezell provide support for the conclusion that one of skill in the art would harbor an expectation of success for the scope of the claims, namely, upon administration of malignin, some inhibition of glioma cancer cells would be expected *in vivo*.

3. The November 30, 2000 Decision from the BPAI Supports Enablement

At the November 20, 2007 Examiner Interview, Examiner Saunders requested Applicant point to support for enablement of the present claims in the November 30, 2000 decision of the Board of Patent Appeals and Interferences in the parent application (U.S. Appln. Ser. No. 08/031,562, now abandoned) of the above-captioned application. The claims under review in the BPAI decision were very broad. *See* BPAI Decision at 9. In fact, the claims were directed to vaccines against "any cancer." *Id.* As such, the BPAI decision does not apply to the present claims, which are directed to glioma cancer, the very cancer from which the malignin peptide was directly isolated.

Because the present claims are directed to inhibition of glioma cells, the Board's findings are, nevertheless, particularly relevant. For example, the Board accepted the accuracy of the Applicant's teaching that higher antimalignin antibody concentrations have been shown to provide longer survival in cancer patients and that lower antimalignin antibody concentrations have resulted from successful cancer treatment. BPAI Decision at 9. Further, the Board's conclusion that undue experimentation was required to practice "the full scope of the claimed invention" does not undermine the present claims since they are directed at glioma cancer cells, cells against which complement dependent cytotoxicity has been directly demonstrated and cells to which *in vivo* binding has been directly observed. As such, the BPAI Decision provides support for the conclusion that the full scope of the present claims is enabled.

CONCLUSION

The Applicant believes the clear teaching of the specification on the cytotoxic and inhibitory character of antimalignin antibody, the *in vivo* binding capacity of the antimalignin antibody, the natural protection provided by the antimalignin antibody in humans, the strong immune response elicited by subcutaneous injection of malignin, the clear teaching of Spitler and Ezell that the very characterizations of the malignin peptide by the Applicant provide an expectation of success to one of skill in the art, and the Board of Patent Appeals and Interference's clear teaching that the November 30, 2000 Decision accepted the data provided in the application (directed most specifically to glioma cells) but did not believe the claims were enabled for any and all cancer types, support a conclusion that the claims as amended are

enabled. As such, it is believed that the present claims are in condition for allowance and Applicant earnestly requests the same. An early and favorable action on the merits is earnestly solicited.

The Examiner is invited to contact the undersigned attorney to expedite allowance. The Commissioner is authorized to charged any fees or overpayments associated with this application to Kenyon & Kenyon LLP **Deposit Account No. 11-0600**.

Respectfully submitted,

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